REMARKS

Status of the claims:

Claims 1-47 are currently pending.

Amendments to the specification:

Applicants have amended the specification to amend a clerical error in which the order of the recitation of two clones HT5EA78 and HCFAZ22 was inadvertantly reversed. Additionally, Applicants have corrected the incorrect recitation of the length of TR11 on page 10. This amendment is supported by SEQ ID NO:2 and Figures 1A-B.

Amendments to the claims:

Applicants have amended claims 19, 33, and 48 (now claim 47) to correct errors arising from the difference in the numbering of the TR11 and TR11SV2 polypeptides as shown in Figures 1A-B and 3A-B, respectively, compared to SEQ ID NOS:2 and 6, respectively. Applicants have also amended the numbering of claims 35-48 as filed on June 4, 2001, because there was no claim 34 and the dependencies were incorrect. Applicants have also amended references in the claims to the ATCC Deposit Numbers and have amended claim 48 (now claim 47) to correct editorial errors. Support for claims 19, 33, and 48 as amended may be found, for example on page 8, lines 1-31, page 61, lines 16-19, SEQ ID NOS:2, 4, and 6 and Figures 1A-B, 2A-B, and 3A-B. Thus no new matter has been added by way of amendment.

CONCLUSION

Applicants respectfully request that the remarks above be entered and made of record in the file history of the instant application.

Respectfully submitted,

Date: August 15, 2001

Jonathan L. Klein (Reg. No. 41,119)
Attorney for Applicants

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850
Phone 301-251-6015

Telecopier Transmission Certificate

Send date:

I hereby certify that this paper and the attachments hereto are being sent by telecopier transmission to **703-308-4426** on the above-indicated date addressed to:

Examiner Anne Holleran • Group 1642
U.S. Patent and Trademark Office
Washington, D.C. 20231

Charissa Pittman August 15, 2001
Name Date

JKE/MS/cmp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ni et al.

Application No.: 09/512,363 Art Unit: 1642

Filed: February 23, 2000 Examiner: Holleran, A

For: Human Tumor Necrosis Factor Receptor-Like Proteins TR11, TR11SV1 and TR11SV2 Atty Docket No.: PF396P1

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments are shown in boldfaced text with insertions indicated by underlining and deletions indicated by strikeout.

In the Specification:

Please replace the paragraph occupying lines 7-25 of page 10 with the following amended paragraph:

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding TR11, TR11SV1, and TR11SV2 polypeptides (Figures 1A and 1B, 2A and 2B, and 3A and 3B (SEQ ID NO:2, SEQ ID NO:4, and SEQ ID NO:6, respectively), the amino acid sequences of which were determined by sequencing cloned cDNAs. The TR11, TR11SV1, and TR11SV2 proteins shown in Figures 1A and 1B, 2A and 2B, and 3A and 3B, respectively, share sequence homology with the human mGITR receptor-like protein (Figure 2 (SEQ ID NO:7)) On October 7, 1997, deposits of plasmid DNAs encoding TR11, TR11SV1, and TR11SV2 were made at the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, and given accession numbers 209341, 209342, and 209343, respectively. The nucleotide sequences shown in Figures 1A and 1B, 2A and 2B, and 3A and 3B (SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5, respectively) were obtained by sequencing cDNA clones (Clone ID HHEAC71, ~~HCFAZ22, and HT5EA78~~, **HT5EA78 and HCFAZ22**, respectively) containing the same amino acid coding sequences as the clones in ATCC Accession Nos. 209341, 209342, and 209343, respectively. The deposited clone

encoding TR11 is contained in the pCMVSport3.0 plasmid (Life Technologies, Rockville, MD). The deposited clone encoding TR11SV1 is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The deposited clone encoding TR11SV2 is contained in the pSport1 plasmid (Life Technologies, Rockville, MD).

Please replace the paragraph starting on line 33 of Page 11 and ending on page 12, line 5, with the following amended paragraph.

The determined nucleotide sequence of the TR11 cDNA of Figures 1A and 1B (SEQ ID NO:1) contains an open reading frame encoding a protein of about ~~241~~ 234 amino acid residues, with a single potential predicted leader sequence of about 25 amino acid residues, and a deduced molecular weight of about 25,113 Da. The amino acid sequence of the potential predicted mature TR11 receptor is shown in Figures 1A and 1B, from amino acid residue about 26 to residue about 234 (amino acid residues 1 to 209 in SEQ ID NO:2). The TR11 protein shown in Figures 1A and 1B (SEQ ID NO:2) is about 58.6% identical and about 74.1% similar to the murine mTIFR receptor protein shown in SEQ ID NO:7 (see Figures 4A and 4B) using the computer program "Bestfit".

Please replace the paragraph spanning lines 1-36 of page 40 with the following amended paragraph.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the TR11, TR11SV1 and/or TR11SV2 polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the TR11, TR11SV1 and/or TR11SV2 polypeptide sequences (e.g., those recited in SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, or contained in the respective TR11, TR11SV1

and TR11SV2 polypeptides encoded by the respective clones HHEAC71, ~~HCFAZ22, and HT5EA78~~ HT5EA78 and HCFAZ22). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a TR11, TR11SV1 or TR11SV2 fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a TR11-Fc, TR11SV1 Fc or TR11SV2-Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more TR11, TR11SV1, TR11SV2 polypeptides of the invention are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include, but are not limited to, those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple TR11, TR11SV1, TR11SV2 polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

Please replace the paragraph beginning on line 33 of page 78 and ending on page 79, line 9 with the following amended paragraph.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in Figures 1A and 1B (SEQ ID NO:2), Figures 2A and 2B (SEQ ID NO:4), and/or Figures 3A and 3B (SEQ ID NO:6), the amino acid sequence encoded by deposited cDNA clones HHEAC71, ~~HT5EA78, and HCFAZ22~~ HT5EA78 and HCFAZ22, respectively, or fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine

whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

Please replace the paragraph spanning lines 17-32 of page 136 with the following amended paragraph

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in TR11, TR11SV1 and/or TR11SV2, or the complementary strand thereof, and/or to nucleotide sequences contained in the deposited clones IMAC71, **HCFAZ22, and ~~HT5EA78~~ HT5EA78 and HCFAZ22**, respectively. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Anitsense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

In the Claims:

Please replace the claims as follows:

19. **(~~New~~ Amended)** A method of inhibiting binding of Endokine-alpha to endogenous Endokine-alpha receptors in a mammal comprising administering to said mammal an effective amount of a TR11 polypeptide selected from the group consisting of:

(a) a polypeptide whose amino acid sequence comprises amino acid residues ~~1-162~~ ~~-25-137~~ of SEQ ID NO:2;

(b) a polypeptide whose amino acid sequence comprises amino acid residues ~~26-162~~ 1-137 of SEQ ID NO:2;

(c) a polypeptide whose amino acid sequence comprises amino acid residues ~~26-139~~ 1-114 of SEQ ID NO:2;

(d) a polypeptide whose amino acid sequence comprises amino acid residues ~~1-164~~ ~~-25-139~~ of SEQ ID NO:2;

(e) a polypeptide whose amino acid sequence comprises amino acid residues ~~46-164~~ 21-139 of SEQ ID NO:2;

(f) a polypeptide whose amino acid sequence comprises amino acid residues ~~33-154~~ 8-129 of SEQ ID NO:2;

(g) a polypeptide whose amino acid sequence comprises amino acid residues ~~33-73~~ 8-48 of SEQ ID NO:2;

(h) a polypeptide whose amino acid sequence comprises amino acid residues ~~74-113~~ 49-88 of SEQ ID NO:2; and

(i) a polypeptide whose amino acid sequence comprises amino acid residues ~~114 to 154~~ 89-129 of SEQ ID NO:2;

in a pharmaceutically acceptable carrier.

73. (~~New~~ Amended) A method of inhibiting binding of Endokine-alpha to endogenous Endokine-alpha receptors in a mammal comprising administering to said mammal an effective amount of a TR11 polypeptide selected from the group consisting of:

B

(a) a polypeptide whose amino acid sequence comprises amino acid residues residues ~~1-162~~ ~~-25-137~~ of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341;

(b) a polypeptide whose amino acid sequence comprises amino acid residues residues ~~26-162~~ 1-137 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341;

(c) a polypeptide whose amino acid sequence comprises amino acid residues ~~26-139~~ 1-114 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341;

(d) a polypeptide whose amino acid sequence comprises amino acid residues ~~1-164~~ ~~-25-139~~ of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341;

(e) a polypeptide whose amino acid sequence comprises amino acid residues ~~46-164~~ 21-139 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341;

(f) a polypeptide whose amino acid sequence comprises amino acid residues ~~33-154~~ 8-129 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341,

(g) a polypeptide whose amino acid sequence comprises amino acid residues ~~33-73~~ 8-48 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341;

(h) a polypeptide whose amino acid sequence comprises amino acid residues ~~74-113~~ 49-88 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341; and

(i) a polypeptide whose amino acid sequence comprises amino acid residues ~~114 to 154~~ 89-129 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209340~~ 209341;

in a pharmaceutically acceptable carrier.

~~35~~ 34. (~~New~~ Amended) The method of claim ~~35~~ 33 wherein the mammal is a human.

~~36~~ 35. (~~New~~ Amended) The method of claim ~~35~~ 33 wherein the TR11 polypeptide is fused to a heterologous polypeptide.

~~37~~ 36. (~~New~~ Amended) The method of claim ~~36~~ 35 wherein the heterologous polypeptide is an immunoglobulin constant domain.

~~38~~ 37. (New Amended) The method of claim ~~37~~ 36 wherein the immunoglobulin constant domain is an IgG1 constant domain.

~~39~~ 38. (~~New~~ Amended) The method of claim ~~37~~ 36 wherein the immunoglobulin constant domain is an IgG3 constant domain.

~~40~~ 39. (~~New~~ Amended) The method of claim 36 35 wherein the heterologous polypeptide is human albumin.

~~41~~ 40. (~~New~~ Amended) The method of claim 35 33 wherein the pharmaceutically acceptable carrier is water.

~~42~~ 41. (~~New~~ Amended) The method of claim ~~35~~ 33 wherein the pharmaceutically acceptable carrier is saline.

~~43~~ 42. (~~New~~ Amended) The method of claim ~~35~~ 33 wherein the pharmaceutically acceptable carrier is Ringer's solution.

~~44~~ 43. (~~New~~ Amended) The method of claim ~~35~~ 33 wherein the pharmaceutically acceptable carrier is dextrose solution.

~~45~~ 44. (~~New~~ Amended) The method of claim ~~35~~ 33 wherein the pharmaceutically acceptable carrier is ethyl oleate.

~~46~~ 45. (New Amended) The method of claim ~~35~~ 33 wherein the pharmaceutically acceptable carrier is a liposome.

~~47~~ 46. (~~New~~ Amended) The method of claim ~~35~~ 33 wherein the TR11 polypeptide inhibits T cell migration across endothelial cells.

~~48~~ 47. (~~New~~ Amended) A method of inhibiting binding of Endokine-alpha to endogenous Endokine-alpha receptors in a mammal comprising administering to said mammal an effective amount of a polypeptide selected from the group consisting of:

(a) a polypeptide whose amino acid sequence comprises amino acid residues 1-162 of SEQ ID NO:4;

B

(b) a polypeptide whose amino acid sequence comprises amino acid residues 1-162 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209341~~ 209342;

(c) a polypeptide whose amino acid sequence comprises amino acid residues ~~1-168~~ -19-149 of ~~the polypeptide encoded by the cDNA contained~~ in ATC~~C Deposit Number 209341~~ SEQ ID NO:6;

(d) a polypeptide whose amino acid sequence comprises amino acid residues ~~20-168~~ 1-149 of ~~the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209342~~ SEQ ID NO:6;

(e) a polypeptide whose amino acid sequence comprises amino acid residues ~~1-168~~ -19-149 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209342~~ 209343; and

(f) a polypeptide whose amino acid sequence comprises amino acid residues ~~20-168~~ 1-149 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number ~~209342~~ 209343;

in a pharmaceutically acceptable carrier.